Paper # 11 Attach

L9 ANSWER 3 OF 24 MEDLINE
AN 1999221891 MEDLINE
DN 99221891
TI Blocking HIV-1 infection with **intrakines** [news].
AU Dorrell S
SO MOLECULAR MEDICINE TODAY, (1999 Mar) 5 (3) 97.
Journal code: CMK. ISSN: 1357-4310.
CY ENGLAND: United Kingdom
DT News Announcement
LA English
FS Priority Journals
EM 199910
EW 19991004

L9 ANSWER 9 OF 24 MEDLINE DUPLICATE 1
AN 1998430728 MEDLINE
DN 98430728
TI Anti-HIV type 1 activity of wild-type and functional defective RANTES **intrakine** in primary human lymphocytes.
AU Yang A G; Zhang X; Torti F; Chen S Y
CS Department of Cancer Biology, Comprehensive Cancer Center, Wake Forest University School of Medicine, Winston-Salem, NC 27157, USA.
NC 1R01-AI41959-01 (NIAID)
SO HUMAN GENE THERAPY, (1998 Sep 20) 9 (14) 2005-18.
Journal code: A12. ISSN: 1043-0342.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199902
EW 19990204
AB We have developed a genetic "**intrakine**" strategy to inactivate the CC-chemokine receptor 5 (CCR-5), the principal coreceptor for macrophage (M)-tropic HIV-1 viruses (Yang et al, 1997).. The inactivation of CCR5 was achieved by targeting a modified CC-chemokine (RANTES) to the lumen of the endoplasmic reticulum (ER) to block the transport of the newly synthesized CCR-5. The transduced lymphocytes with the phenotypic CCR5 knockout were shown to be resistant to M-tropic HIV-1 infection. This study illustrated the feasibility of the **intrakine** strategy to block HIV-1 infection. In our current study, the potential clinical application of the **intrakine** approach was further evaluated in human peripheral blood lymphocytes (PBLs). PBLs were transduced with the RANTES **intrakine** gene by using retroviral vectors with the truncated low-affinity human nerve growth factor receptor (deltaNGFR) marker, and then isolated by an anti-NGFR antibody/magnetic bead method. The surface expression of CCR-5 in the transduced lymphocytes was dramatically inhibited, as demonstrated by flow cytometric assays. The transduced PBLs were shown to resist various types of M-tropic HIV-1 virus infection. The cell viability, cell proliferation rates, and cell surface markers of the **intrakine**-transduced PBLs were shown to be comparable to those of control PBLs. The transduced PBLs were also found to respond to the stimulation of various CXC- and CC-chemokines, other than RANTES. The transduced PBLs responded to tetanus antigen stimulation by increasing IL-2 production and cell proliferation. In addition, a functionally defective mutant of RANTES that retains its binding activity

to CCR-5, but loses its signaling ability, was used to generate a mutant RANTES **intrakine**. The primary lymphocytes transduced with the mutant RANTES **intrakine** were found to be resistant to M-tropic HIV-1 infection. From these results, we conclude that the primary human lymphocytes transduced with either the wild-type or functionally defective RANTES **intrakine** are resistant to M-tropic HIV-1 infection, and maintain their basic biological functions. This study, therefore, indicates the potential clinical application of the **intrakine** approach for HIV-1 gene therapy.

L9 ANSWER 10 OF 24 MEDLINE DUPLICATE 2
AN 1999031213 MEDLINE
DN 99031213
TI Genetic co-inactivation of macrophage- and T-tropic HIV-1 chemokine coreceptors CCR-5 and CXCR-4 by **intrakines**.
AU Bai X; Chen J D; Yang A G; Torti F; Chen S Y
CS Department of Cancer Biology, Comprehensive Cancer Center, Wake Forest University School of Medicine, Winston-Salem, NC 27157, USA.
NC R01-AL41959-01
SO GENE THERAPY, (1998 Jul) 5 (7) 984-94.
Journal code: CCE. ISSN: 0969-7128.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199902
EW 19990204
AB CC-chemokine receptor (CCR)-5 is the principal coreceptor for the entry of macrophage (M)-tropic HIV-1 viruses into a cell, while CXC-chemokine receptor (CXCR)-4 is the principal coreceptor for T cell line (T)-tropic HIV-1. In this study, we utilized a novel intracellular chemokine (**intrakine**) strategy to co-inactivate genetically both CCR-5 and CXCR-4 in human lymphocytes. The principle of co-inactivation of CCR-5 and CXCR-4 was illustrated by targeting the CC-**intrakine** and CXC-**intrakine** to the lumen of the endoplasmic reticulum (ER) for intracellular blockade of the transport of newly synthesized chemokine coreceptors to the cell surface. The lymphocytes with the phenotypic knock-out of CCR-5 and CXCR-4 were found broadly to resist the infection of M-tropic, T-tropic and dual-tropic HIV-1 viruses. Moreover, the transduced lymphocytes retained normal cell features, including the responsiveness to mitogen and recall antigen stimulation. Thus, this study to our knowledge, is the first to demonstrate that genetic co-inactivation of the M- and T-tropic HIV-1 principal coreceptors in lymphocytes or other cells could be a viable strategy for the long-term control of HIV-1 infection.

L9 ANSWER 11 OF 24 MEDLINE DUPLICATE 3
AN 1998126121 MEDLINE
DN 98126121
TI **Intrakines** and blocking HIV infection: abstract and commentary.
AU D'Souza P
CS Pathogenesis and Basic Research Branch, Division of AIDS, NIAID, National Institutes of Health, Bethesda, Md, USA.. pd6n@nih.gov
SO JAMA, (1998 Feb 11) 279 (6) 476.
Journal code: KFR. ISSN: 0098-7484.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals

EM 199804
EW 19980403

L9 ANSWER 12 OF 24 MEDLINE DUPLICATE 4
AN 97471007 MEDLINE
DN 97471007
TI Phenotypic knockout of HIV type 1 chemokine coreceptor CCR-5 by **intrakines** as potential therapeutic approach for HIV-1 infection.
AU Yang A G; Bai X; Huang X F; Yao C; Chen S
CS Department of Cancer Biology, Comprehensive Cancer Center, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, NC 27157, USA.
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1997 Oct 14) 94 (21) 11567-72.
Journal code: PV3. ISSN: 0027-8424.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199801
EW 19980104
AB A genetic defect in a CC-chemokine receptor (CCR)-5, the principal coreceptor for the macrophage-tropic HIV type 1 (HIV-1), recently was found to naturally protect CCR-5-defective, but healthy, individuals from HIV-1 infection. In this study, we mimic the natural resistance of the CCR-5-defective individuals by designing a strategy to phenotypically knock out CCR-5. The inactivation of the CCR-5 coreceptor is accomplished by targeting a modified CC-chemokine to the endoplasmic reticulum to block the surface expression of newly synthesized CCR-5. The lymphocytes transduced to express the intracellular chemokine, termed "**intrakine**," were found to be viable and resistant to macrophage-tropic HIV-1 infection. Thus, this gene-based **intrakine** strategy targeted at the conserved cellular receptor for the prevention of HIV-1 entry should have significant advantages over currently described approaches for HIV-1 therapy.

L9 ANSWER 13 OF 24 MEDLINE DUPLICATE 5
AN 97475198 MEDLINE
DN 97475198
TI Inactivation of HIV-1 chemokine co-receptor CXCR-4 by a novel **intrakine** strategy [see comments].
CM Comment in: Nat Med 1997 Oct;3(10):1074-5
AU Chen J D; Bai X; Yang A G; Cong Y; Chen S Y
CS Department of Cancer Biology, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, North Carolina 27157, USA.
SO NATURE MEDICINE, (1997 Oct) 3 (10) 1110-6.
Journal code: CG5. ISSN: 1078-8956.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199801
EW 19980104
AB CXC-chemokine receptor (CXCR)-4/fusin, a newly discovered co-receptor for T-cell line (T)-tropic HIV-1 virus, plays a critical role in T-tropic virus fusion and entry into permissive cells. The occurrence of T-tropic HIV viruses is associated with CD4-positive cell decline and progression to AIDS, suggesting that the T-tropic HIV-1 contributes to AIDS pathogenesis. In this study, we used a novel strategy to inactivate CXCR-4 by targeting a modified CXC-chemokine to the endoplasmic reticulum (ER) to block the surface expression of newly synthesized CXCR-4. The genetically

modified lymphocytes expressing this intracellular chemokine, termed "**intrakine**", are immune to T-tropic virus infection and appear to retain normal biological features. Thus, this genetic **intrakine** strategy is uniquely targeted at the conserved cellular receptor for the prevention of HIV-1 entry and may be developed into an effective treatment for HIV-1 infection and AIDS.

L9 ANSWER 14 OF 24 CAPLUS COPYRIGHT 2000 ACS
AN 1997:658824 CAPLUS
DN 127:330222
TI A chemokine trap for HIV co-receptors
AU Lusso, Paolo
CS Dep. Biologial and Technological Res., San Raffaele Scientific Inst., Milan, 20132, Italy
SO Nat. Med. (N. Y.) (1997), 3(10), 1074-1075
CODEN: NAMEFI; ISSN: 1078-8956
PB Nature America
DT Journal
LA English
AB A discussion of the novel anti-HIV strategy of Chen, J.-D., et al., (1997) which uses modified chemokines (**intrakines**), trapped within the endoplasmic reticulum, to block expression of HIV co-receptors on the host cell surface. The purpose of jamming the cell's ER with a crowd of modified chemokines is that the entrapped stromal cell-derived factor-1 (SDF-1) will form intracellular complexes with newly synthesized CXCR4 proteins in the ER, preventing them from reaching the cell surface. Here, P. Lusso indicates some of the problems in adapting the system to in vivo results, including specificity and efficiency of transduction, expression of the therapeutic genes, retroviral vectors, and the immunol. competence of the transduced lymphocytes, following their reinfusion into the patient. However, a combination of therapeutic tools (drugs or genes) interfering with the viral life-cycle at several levels, may succeed in maintaining the level of viral replication below the threshold of immunol. damage.

L21 ANSWER 23 OF 77 MEDLINE DUPLICATE 15
AN 96161997 MEDLINE
DN 96161997
TI Extension of recombinant human **RANTES** by the **retention** of the initiating methionine produces a potent antagonist.
AU Proudfoot A E; Power C A; Hoogewerf A J; Montjovent M O; Borlat F; Offord R E; Wells T N
CS Glaxo Institute for Molecular Biology, Geneva, Switzerland.. AEP6830@ggh.uk.co
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1996 Feb 2) 271 (5) 2599-603. Journal code: HIV. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199605
AB Extension of recombinant human **RANTES** by a single residue at the amino terminus is sufficient to produce a potent and selective antagonist.

RANTES is a proinflammatory cytokine that promotes cell accumulation and activation in chronic inflammatory diseases. When mature **RANTES** was expressed heterologously in Escherichia coli, the amino-terminal initiating methionine was not removed by the endogenous amino peptidases. This methionylated protein was fully folded but completely inactive in **RANTES** bioassays of calcium mobilization and chemotaxis of the promonocytic cell line THP-1. However, when assayed as an antagonist of both **RANTES** and macrophage inflammatory polypeptide-1 alpha (**MIP**-1 alpha) in these assays, the methionylated **RANTES** (Met-**RANTES**) inhibited the actions of both **chemokines**. T cell chemotaxis was similarly inhibited. The antagonistic effect was selective since Met-**RANTES** had no effect on interleukin-8- or monocyte chemotractant protein-1-induced responses in these cells. Met-**RANTES** can compete with both [125I]**RANTES** and [125I]IMP-1 alpha binding to THP-1 cells or to stably transfected HEK cells recombinantly expressing their common receptor, CC-CKR-1. These data show that the integrity of the amino terminus of **RANTES** is crucial to receptor binding and cellular activation.

L26 ANSWER 3 OF 15 MEDLINE DUPLICATE 1
AN 1998031948 MEDLINE
DN 98031948
TI Defects in macrophage recruitment and host defense in mice lacking the CCR2 **chemokine** receptor.
AU Kurihara T; Warr G; Loy J; Bravo R
CS Department of Oncology, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, New Jersey 08543-4000, USA.
SO JOURNAL OF EXPERIMENTAL MEDICINE, (1997 Nov 17) 186 (10) 1757-62. Journal code: I2V. ISSN: 0022-1007.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199802
EW 19980204
AB **Chemokines** are a structurally related family of cytokines that are important for leukocyte trafficking. The C-C **chemokine** monocyte chemoattractant protein-1 (MCP-1) is a potent monocyte activator in vitro and has been associated with monocytic infiltration in several inflammatory diseases. One C-C **chemokine** receptor, CCR2, has been identified that mediates in vitro responses to MCP-1 and its close structural homologues. CCR2 has also recently been demonstrated to be a **fusion** cofactor for several HIV isolates. To investigate the normal physiological function of CCR2, we generated mice with a targeted disruption of the ccr2 **gene**. Mice deficient for CCR2 developed normally and had no hematopoietic abnormalities. However, ccr2(-/-) mice failed to recruit macrophages in an experimental peritoneal inflammation model. In addition, these mice were unable to clear infection by the **intracellular** bacteria, Listeria monocytogenes. These results suggest that CCR2 has a nonredundant role as a major mediator of macrophage recruitment and host defense against bacterial pathogens and that MCP-1 and other CCR2 ligands are effectors of those functions.

L33 ANSWER 13 OF 128 MEDLINE DUPLICATE 7
AN 1998063063 MEDLINE
DN 98063063
TI Impaired monocyte migration and reduced type 1 (Th1) cytokine responses in
C-C **chemokine** receptor 2 **knockout** mice.
AU Boring L; Gosling J; Chensue S W; Kunkel S L; Farese R V Jr; Broxmeyer H E; Charo I F
CS Gladstone Institute of Cardiovascular Disease, University of California, San Francisco 94141-9100, USA.
NC HL-52773 (NHLBI)
DK-53674 (NIDDK)
HL-56416 (NHLBI)
SO JOURNAL OF CLINICAL INVESTIGATION, (1997 Nov 15) 100 (10) 2552-61.
Journal code: HS7. ISSN: 0021-9738.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 199803
EW 19980303
AB Monocyte chemoattractant protein-1 (MCP-1) is a potent agonist for mononuclear leukocytes and has been implicated in the pathogenesis of atherosclerosis and granulomatous lung disease. To determine the role of MCP-1 and related family members in vivo, we used homologous recombination
in embryonic stem cells to generate mice with a targeted **disruption** of C-C **chemokine** receptor 2 (CCR2), the receptor for MCP-1. CCR2-/- mice were born at the expected Mendelian ratios and developed normally. In response to thioglycollate, the recruitment of peritoneal macrophages decreased selectively. In in vitro chemotaxis assays, CCR2-/- leukocytes failed to migrate in response to MCP-1. Granulomatous lung disease was induced in presensitized mice by embolization with beads coupled to purified protein derivative (PPD) of Mycobacterium bovis. As compared with wild-type littermates, CCR2-/- mice had a decrease in granuloma size accompanied by a dramatic decrease in the
level of interferon gamma in the draining lymph nodes. Production of interferon gamma was also decreased in PPD-sensitized splenocytes from CCR2-/- mice and in naive splenocytes activated by concanavalin A. We conclude that CCR2-/- mice have significant defects in both delayed-type hypersensitivity responses and production of Th1-type cytokines. These data suggest an important and unexpected role for CCR2 activation in modulating the immune response, as well as in recruiting monocytes/macrophages to sites of inflammation.

L33 ANSWER 15 OF 128 MEDLINE DUPLICATE 8
AN 97474771 MEDLINE
DN 97474771
TI Targeted **disruption** of the beta-**chemokine** receptor **CCR1** protects against pancreatitis-associated lung injury.
AU Gerard C; Frossard J L; Bhatia M; Saluja A; Gerard N P; Lu B; Steer M
CS Ina Sue Perlmutter Laboratory, Children's Hospital, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School and
the Center for Blood Research, Boston, Massachusetts 02115, USA.
NC AI-39759 (NIAID)
HL-52503 (NHLBI)

DK-31396 (NIDDK)
SO JOURNAL OF CLIN[redacted]L INVESTIGATION, (1997 Oct 15) [redacted]0 (8) 2022-7.
Journal code: HS7. ISSN: 0021-9738.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 199801
EW 19980104
AB beta-**Chemokines** and their receptors mediate the trafficking and activation of a variety of leukocytes including the lymphocyte and macrophage. An array of no less than eight beta-**chemokine** receptors has been identified, four of which are capable of recognizing the **chemokines MIP1alpha** and **RANTES**. Genetic deletion of one of the **MIP1alpha** and **RANTES** receptors, **CCR5**, is associated with protection from infection with HIV-1 in humans, while deletion of the ligand **MIP1alpha** protects against Coxsackie virus-associated myocarditis. In this report we show that the deletion of another receptor for **MIP1alpha** and **RANTES**, the **CCR1** receptor, is associated with protection from pulmonary inflammation secondary to acute pancreatitis in the mouse. The protection from lung injury is associated with decreased levels of TNF-alpha in a temporal sequence indicating that the activation of the **CCR1** receptor is an early event in the systemic inflammatory response syndrome.

L33 ANSWER 16 OF 128 MEDLINE DUPLICATE 9
AN 97311094 MEDLINE
DN 97311094
TI Impaired host defense, hematopoiesis, granulomatous inflammation and type 1-type 2 cytokine balance in mice lacking CC **chemokine** receptor 1.
AU Gao J L; Wynn T A; Chang Y; Lee E J; Broxmeyer H E; Cooper S; Tiffany H L; Westphal H; Kwon-Chung J; Murphy P M
CS Laboratory of Host Defenses,National Institute of Allergy and Infectio us Diseases, National Institutes of Health, Bethesda, Maryland 20892, USA.
NC R01 HL56416 (NHLBI)
R01 HL54037 (NHLBI)
P01 HL53586 (NHLBI)
SO JOURNAL OF EXPERIMENTAL MEDICINE, (1997 Jun 2) 185 (11) 1959-68.
Journal code: I2V. ISSN: 0022-1007.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199709
EW 19970901
AB CC **chemokine** receptor 1 (**CCR1**) is expressed in neutrophils, monocytes, lymphocytes, and eosinophils, and binds the leukocyte chemoattractant and hematopoiesis regulator macrophage inflammatory protein (**MIP**)-1alpha, as well as several related CC **chemokines**. Four other CCR subtypes are known; their leukocyte and **chemokine** specificities overlap with, but are not identical to, **CCR1**, suggesting that **CCR1** has both redundant and specific biologic roles. To test this, we have developed **CCR1** -deficient mice (-/-) by targeted gene **disruption**. Although the distribution of mature leukocytes was normal, steady state and induced trafficking and proliferation of myeloid progenitor cells were disordered in -/- mice. Moreover, mature neutrophils from -/- mice failed to chemotax in vitro and failed to mobilize into peripheral blood in vivo in response to **MIP**-1alpha. Consistent with this, -/- mice had accelerated mortality when challenged with Aspergillus fumigatus, a fungus controlled principally by neutrophils. To test the role of **CCR1** in

granuloma formation, we injected Schistosoma mansoni eggs intravenously, and observed a [redacted] reduction in the size of lung [redacted]anulomas in -/- mice compared to +/+ littermates. This was associated with increased interferon-gamma and decreased interleukin-4 production in -/- versus +/+ lung lymph node cells stimulated with egg-specific antigen, suggesting that **CCR1** influences the inflammatory response not only through direct effects on leukocyte chemotaxis, but also through effects on the type 1-type 2 cytokine balance. Thus **CCR1** has nonredundant functions in hematopoiesis, host defense, and inflammation.

L33 ANSWER 17 OF 128 MEDLINE DUPLICATE 10
AN 1998031948 MEDLINE
DN 98031948
TI Defects in macrophage recruitment and host defense in mice lacking the CCR2 **chemokine** receptor.
AU Kurihara T; Warr G; Loy J; Bravo R
CS Department of Oncology, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, New Jersey 08543-4000, USA.
SO JOURNAL OF EXPERIMENTAL MEDICINE, (1997 Nov 17) 186 (10) 1757-62. Journal code: I2V. ISSN: 0022-1007.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199802
EW 19980204
AB **Chemokines** are a structurally related family of cytokines that are important for leukocyte trafficking. The C-C **chemokine** monocyte chemoattractant protein-1 (MCP-1) is a potent monocyte activator in vitro and has been associated with monocytic infiltration in several inflammatory diseases. One C-C **chemokine** receptor, CCR2, has been identified that mediates in vitro responses to MCP-1 and its close structural homologues. CCR2 has also recently been demonstrated to be a fusion cofactor for several HIV isolates. To investigate the normal physiological function of CCR2, we generated mice with a targeted **disruption** of the ccr2 gene. Mice deficient for CCR2 developed normally and had no hematopoietic abnormalities. However, ccr2(-/-) mice failed to recruit macrophages in an experimental peritoneal inflammation model. In addition, these mice were unable to clear infection by the intracellular bacteria, Listeria monocytogenes. These results suggest that CCR2 has a nonredundant role as a major mediator of macrophage recruitment and host defense against bacterial pathogens and that MCP-1 and other CCR2 ligands are effectors of those functions.

L33 ANSWER 20 OF 128 MEDLINE DUPLICATE 13
AN 1998053818 MEDLINE
DN 98053818
TI New strategies for **chemokine** inhibition and modulation: you take the high road and I'll take the low road.
AU McFadden G; Kelvin D
CS Department of Microbiology and Immunology, University of Western Ontario, London, Canada.. mcfadden@rri.on.ca
SO BIOCHEMICAL PHARMACOLOGY, (1997 Dec 15) 54 (12) 1271-80. Ref: 94 Journal code: 9Z4. ISSN: 0006-2952.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals; Cancer Journals
EM 199802
EW 19980204

AB **Chemokines** are low molecular weight cytokines that induce extravasation, [redacted]motaxis, and activation of a w[redacted] variety of leukocytes.

Members of the different **chemokine** families are defined by the orientation of specific critical cysteine residues, and are designated as C-X-C (e.g. interleukin-8), C-C (e.g. regulated upon activation normally T

cell expressed and secreted, **RANTES**), or C (lymphotactin). All **chemokines** bind to members of a G-protein coupled serpentine receptor superfamily that span the leukocyte cell surface membrane seven times and mediate the biological activities of the individual ligands. Most **chemokines** possess two major binding surfaces: a high affinity site responsible for specific ligand/receptor interactions and a lower affinity site, also called the heparin-binding or glycosaminoglycan-binding domain, believed to be responsible for the establishment and presentation of **chemokine** gradients on the surface of endothelial cells and within the extracellular matrix. Although

chemokines are clearly beneficial in wound healing, hemopoiesis, and the clearance of infectious organisms, the continued expression of **chemokines** is associated with chronic inflammation. Therefore, this class of cytokines are attractive targets for the creation of antagonists that abrogate one or more **chemokine** functions. It is envisioned that such antagonists could serve as a new class of anti-inflammatory drugs. In this commentary, we will discuss two different

but related strategies for antagonizing **chemokine**-induced functions, namely, **disruption** of the low and high affinity binding sites.

L33 ANSWER 24 OF 128 MEDLINE DUPLICATE 16
AN 97223828 MEDLINE
DN 97223828
TI IL-8 **single-chain** homodimers and heterodimers: interactions with **chemokine** receptors CXCR1, CXCR2, and DARC.
AU Leong S R; Lowman H B; Liu J; Shire S; Deforge L E; Gillece-Castro B L; McDowell R; Hebert C A
CS Department of Immunology, Genentech, Inc., South San Francisco, California
94080, USA.
SO PROTEIN SCIENCE, (1997 Mar) 6 (3) 609-17.
Journal code: BNW. ISSN: 0961-8368.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199707
EW 19970705
AB Covalent **single-chain** dimers of the **chemokine** interleukin-8 (IL-8) have been designed to mimic the dimeric form of IL-8 in solution and facilitate the production of heterodimer variants of IL-8.

Physical studies indicated that use of a simple peptide linker to join two

subunits, while allowing receptor binding and activation, led to self-association of the tethered dimers. However, addition of a single disulfide crosslink between the tethered subunits prevented this multimer from forming, yielding a species of dimer molecular weight. Crosslinked **single-chain** dimers bind to both IL-8 neutrophil receptors CXCR1 and CXCR2 as well as to DARC, as does a double disulfide-linked dimer with no peptide linker. In addition, neutrophil response to these dimers as measured by chemotaxis or beta-glucuronidase release is similar to that elicited by wild-type IL-8, providing evidence that the dissociation of the dimeric species is not required for these biologically relevant activities. Finally, through construction of

single-chain heterodimer mutants, we show that only the first subunit's [redacted]R motif is the **single-chain** [redacted] variants.

L33 ANSWER 30 OF 128 MEDLINE DUPLICATE 20
AN 97386611 MEDLINE
DN 97386611
TI The amino-terminal domain of the CCR2 **chemokine** receptor acts as coreceptor for HIV-1 infection.
AU Frade J M R; Llorente M; Mellado M; Alcami J; Gutierrez-Ramos J C; Zaballos A; Real G; Martinez-A C
CS Department of Immunology and Oncology, Centro Nacional de Biotecnologia, Consejo Superior de Investigaciones Cientificas, Universidad Autonoma de Madrid, Campus de Cantoblanco, E-28049 Madrid, Spain.
SO JOURNAL OF CLINICAL INVESTIGATION, (1997 Aug 1) 100 (3) 497-502. Journal code: HS7. ISSN: 0021-9738.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 199711
EW 19971101
AB The **chemokines** are a homologous serum protein family characterized by their ability to induce activation of integrin adhesion molecules and leukocyte migration. **Chemokines** interact with their receptors, which are composed of a **single-chain**, seven-helix, membrane-spanning protein coupled to G proteins. Two CC **chemokine** receptors, **CCR3** and **CCR5**, as well as the CXCR4 **chemokine** receptor, have been shown necessary for infection by several HIV-1 virus isolates. We studied the effect of the **chemokine** monocyte chemoattractant protein 1 (MCP-1) and of a panel of MCP-1 receptor (CCR2)-specific monoclonal antibodies (mAb) on the suppression of HIV-1 replication in peripheral blood mononuclear cells. We have compelling evidence that MCP-1 has potent HIV-1 suppressive activity when HIV-1-infected peripheral blood lymphocytes are used as target cells. Furthermore, mAb specific for the MCP-1R CCR2 which recognize the third extracellular CCR2 domain inhibit all MCP-1 activity and also block MCP-1 suppressive activity. Finally, a set of mAb specific for the CCR2 amino-terminal domain, one of which mimics MCP-1 activity, has a potent suppressive effect on HIV-1 replication in M- and T-tropic HIV-1 viral isolates. We conjecture a role for CCR2 as a coreceptor for HIV-1 infection and map the HIV-1 binding site to the amino-terminal part of this receptor. This concurs with results showing that the **CCR5** amino terminus is relevant in HIV-1 infection, although chimeric fusion of various extracellular domains shows that other domains are also implicated. We discuss the importance of CCR2 structure relative to its coreceptor role and the role of anti-CCR2 receptor antibodies in the prevention of HIV-1 infection.

L33 ANSWER 43 OF 128 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
AN 97308933 EMBASE
DN 1997308933
TI [13] Gene targeting strategies to study **chemokine** function in vivo.
AU Cook D.N.
CS D.N. Cook, Department of Immunology, Schering-Plough Research Inst., Kenilworth, NJ 07033, United States
SO Methods in Enzymology, (1997) 287/- (186-206). ISSN: 0076-6879 CODEN: MENZAU
CY United States
DT Journal; Article

FS 029 Clinical Biochemistry
LA English

L33 ANSWER 79 OF 128 CAPLUS COPYRIGHT 2000 ACS
AN 1998:521376 CAPLUS
DN 129:301259
TI Genetic approaches to the study of **chemokine** function in vivo
AU Cook, Donald N.; Lira, Sergio A.
CS Department of Pathology, University of North Carolina, Chapel Hill, NC, USA
SO Leukocyte Recruitment Inflammatory Dis. (1996), 259-271. Editor(s): Peltz, Gary. Publisher: Landes, Austin, Tex.
CODEN: 66ODAR
DT Conference; General Review
LA English
AB A review with 60 refs. Topics discussed include an overview of transgene and gene **knockout** technol.; mice expressing **chemokine** transgenes; and anal. of interleukin-8 receptor homolog and **MIP** -1.alpha. **knockout** mice.

L33 ANSWER 88 OF 128 CAPLUS COPYRIGHT 2000 ACS
AN 1995:896295 CAPLUS
DN 123:309606
TI **Antisense** oligonucleotide to **chemokine** for therapeutic treatment of vascular restenosis
IN Lyle, Leon R.; Thomas-Miller, Beth
PA Mallinckrodt Medical, Inc., USA
SO PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9519167	A1	19950720	WO 1995-US605	19950113
W: CA, JP, MX				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2181035	AA	19950720	CA 1995-2181035	19950113
JP 09508358	T2	19970826	JP 1995-519178	19950113
EP 802792	A1	19971029	EP 1995-908532	19950113
R: DE, FR				

PRAI US 1994-182917 19940114
WO 1995-US605 19950113
OS MARPAT 123:309606
AB A compn. suitable for administration to a warm-blooded animal is disclosed which comprises an **antisense** oligonucleotide to the C-C **chemokine** family, typified by MCP-1 and **MIP**-1.alpha., which may or may not be labeled with a radionuclide by means of a chelate ligand capable of administration to an animal to produce reliable visual imaging of areas of potential restenosis or to produce therapeutic effects on areas of potential restenosis.

L33 ANSWER 92 OF 128 MEDLINE DUPLICATE 55
AN 95397153 MEDLINE
DN 95397153
TI Requirement of **MIP**-1 alpha for an inflammatory response to viral infection.
AU Cook D N; Beck M A; Coffman T M; Kirby S L; Sheridan J F; Pragnell I B; Smithies O
CS Department of Pathology, University of North Carolina, Chapel Hill 27599-7525, USA.
NC GM20069 (NIGMS)
HL37001 (NHLBI)

R29HL46195 (NHLBI)
SO SCIENCE, (1995 [redacted] 15) 269 (5230) 1583-5.
Journal code: U[redacted]. ISSN: 0036-8075.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199512
AB Macrophage inflammatory protein-1 alpha (**MIP**-1 alpha) is a **chemokine** that has pro-inflammatory and stem cell inhibitory activities in vitro. Its biologic role in vivo was examined in mice in which the gene encoding **MIP**-1 alpha had been **disrupted**. Homozygous **MIP**-1 alpha mutant (-/-) mice were resistant to Coxsackievirus-induced myocarditis seen in infected wild-type (+/+) mice. Influenza virus-infected -/- mice had reduced pneumonitis and delayed clearance of the virus compared with infected +/+ mice. The -/- mice had no overt hematopoietic abnormalities. These results demonstrate that **MIP**-1 alpha is an important mediator of virus-induced inflammation in vivo.

L33 ANSWER 102 OF 128 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1995:381289 BIOSIS
DN PREV199598395589
TI Role of **MIP**-1-alpha in pulmonary inflammation during an influenza viral infection: Analysis in a **MIP**-1-alpha **knockout** mouse model.
AU Cook, D.; Beck, M. A.; Jung, J.; Smithies, O.; Sheridan, J. F.
CS Univ. North Carolina, Chapel Hill, NC USA
SO 9TH INTERNATIONAL CONGRESS OF IMMUNOLOGY.. (1995) pp. 114. The 9th International Congress of Immunology.
Publisher: 9th International Congress of Immunology San Francisco, California, USA.
Meeting Info.: Meeting Sponsored by the American Association of Immunologists and the International Union of Immunological Societies San Francisco, California, USA July 23-29, 1995
DT Conference
LA English

L33 ANSWER 107 OF 128 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1994:518777 BIOSIS
DN PREV199497531777
TI **Disruption** of the Scya5/**RANTES** gene by homologous recombination.
AU Danoff, Theodore M.; Chiang, Mark Y.; Neilson, Eric G.
CS Penn Center Mol. Studies Kidney Diseases, Renal Electrolyte Hypertension Div., University Pennslyvania, Philadelphia, PA USA
SO Journal of the American Society of Nephrology, (1994) Vol. 5, No. 3, pp. 744.
Meeting Info.: Abstracts Submitted for the 27th Annual Meeting of the American Society of Nephrology Orlando, Florida, USA October 26-29, 1994
ISSN: 1046-6673.
DT Conference
LA English

L33 ANSWER 110 OF 128 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1994:151108 BIOSIS
DN PREV199497164108
TI **Disruption** of the SCI/**MIP** 1-alpha gene by homologous recombination.
AU Cook, Don N. (1); Coffman, Tom; Kirby, Suzanne L. (1); Plumb, Mark; Pragnell, Ian B.; Smithies, Oliver (1)
CS (1) Dep. Pathol., Univ. North Carolina at Chapel Hill, Chapel Hill, NC USA
SO Journal of Cellular Biochemistry Supplement, (1994) Vol. 0, No. 18 PART A,

pp. 24.
Meeting Info.: [redacted]stone Symposium on Hematopoies[redacted]Breckenridge, Colorado,
USA January 4-11, 1994
ISSN: 0733-1959.
DT Conference
LA English

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=> d his

     (FILE 'HOME' ENTERED AT 11:25:08 ON 24 MAY 2000)

     FILE 'MEDLINE, BIOSIS, EMBASE, CAPLUS' ENTERED AT 11:25:12 ON 24 MAY 2000
L1        266978 S HIV
L2        241931 S HUMAN IMMUNODEFICIENCY VIRUS
L3        324183 S L1 OR L2
L4          5177 S CORECEPTOR? OR (CO RECEPTOR?)
L5          2715 S L3 AND L4
L6           692 S L5 NOT PY>1997
L7         24489 S CHEMOKINE?
L8            37 S INTRAKINE?
L9            24 DUP REM L8 (13 DUPLICATES REMOVED)
L10         4058 S CCR5 OR CCR3 OR CCR1 OR CXR4
L11          616 S CCR (W)(1 OR 3 OR 5)
L12            1 S CXR(W) 4
L13        14862 S RANTES OR MIP OR MIP1? OR SDF
L14        32902 S L7 OR L10 OR L11 OR L12 OR L13
L15        16634 S L14 NOT PY>1997
L16       316901 S (SIGNAL SEQUENCE?) OR (SIGNAL PEPTIDE?) OR RETENTION
L17          188 S L15 AND L16
L18       230689 S (ENDOPLASMIC RETICULUM) OR GOLGI OR LYSOSOME?
L19       869791 S VESICLE? OR ORGANELLE? OR INTRACELLULAR
L20         1032 S L15 AND (L18 OR L19)
L21           77 DUP REM L17 (111 DUPLICATES REMOVED)
L22          289 S L20 AND (GENE OR CDNA OR VECTOR OR CONSTRUCT)
L23          109 S L20 AND DNA
L24          306 S L22 OR L23
L25           26 S L24 AND (FUSED OR FUSION OR HYBRID OR CHIMERIC)
L26           15 DUP REM L25 (11 DUPLICATES REMOVED)
L27        15710 S SINGLE CHAIN
L28          147 S INTRABOD?
L29        50848 S ANTISENSE
L30       240076 S KNOCKOUT? OR DISRUPT?
L31       304917 S L27 OR L28 OR L29 OR L30
L32          309 S L15 AND L31
L33          128 DUP REM L32 (181 DUPLICATES REMOVED)
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